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| EXAMINER |
|---|
| WELLS, LAUREN Q |

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| 1617 | 22 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/519,998 | Applicant(s) WILBUR ET AL. | |
|---|---|---|---|
| | Examiner Lauren Q Wells | Art Unit 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-9,11-22 and 24-39* is/are pending in the application.

4a) Of the above claim(s) *26-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-22,24,25 and 31-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Claims 1-9, 11-22, and 24-39 are pending. Claims 26-27 and 28-30 are withdrawn from consideration, as they are directed toward non-elected subject matter. The Amendment filed 6/26/03, Paper NO. 21, amended claims 1 and 7.

### *Election/Restrictions*

The Election of Species requirement of 6/4/03, Paper No. 20, is hereby withdrawn. The claims of Group I have been searched in their entirety.

Applicant's election with traverse of the Restriction Requirement in Paper No. 21 is acknowledged. The traversal is on the ground(s) that a search for the claims in the remaining groups would not be substantially burdensome after a search for the claims in Group I. This argument is not persuasive, as a method of diagnosis/treatment and a kit, require completely different searches that would be burdensome. It is respectfully pointed out that searching a structure does not result in a parallel search for a method of diagnosis/treatment or a kit.

The requirement is still deemed proper and is therefore made FINAL.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11-22, 24-25, 31-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for diagnosis of myocardial infarction and certain cancers and treatment of certain cancers, does not reasonably provide enablement for diagnosis and treatment of human and animal conditions or diseases. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention provides a molecule of formula (I) with at least three functional parts comprising a trifunctional cross-linking moiety that is linked via an optional linker to an affinity ligand, a biomolecule reactive moiety, and an effector agent.

(2) The state of the prior art

The prior art teaches trifunctional compounds as recited in instant claim 1. However, the art does not teach all the possible compounds encompassed by formula (I) of instant claim 1. See WO 97/29114. Additionally, WO 97/29114 teach that one compounds of formula (I) can be used for the diagnosis of certain cancers and myocardial infarcts and the treatment of certain cancers.

(3) The relative skill of those in the art

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art

The unpredictability of the art is very high, as a method of diagnosing or treating one disease or condition does not necessitate the treatment or diagnosis of another disease or condition, since diseases and conditions have unique chemical pathways by which they are expressed. Additionally, a single disease or condition can be diagnosed via multiple biochemical pathways and treated via multiple biochemical pathways. Thus, the treatment and diagnosis of disorders and conditions is highly unpredictable.

(5) The breadth of the claims

The claims are very broad. First, the trifunctional cross-linking moiety is anything that can bind to three different compounds. The affinity ligand binds to anything that is an amide bond and that is stabilized towards enzymatic cleavage. The effector agent is anything that exerts an effect on cells, tissues, and/or humorous molecules in vivo or ex vivo. The biomolecule reactive moiety is anything that forms a bond between the reagent and the biomolecule. Additionally, any linker can be placed between the cross-linking moiety and each

of the three constituents. Also, this compound can be used to treat OR diagnose ANY disease or disorder.

(6) The amount of direction or guidance presented

Pages 2-3 of the specification provide support for the diagnosis of myocardial infarcts and for the diagnosis and treatment of the cancers recited on pages 2-3. However, this is the only guidance the specification presents regarding the diseases and conditions that can be diagnosed or treated using the instant compound of formula (I). The remainder of the specification is directed toward the specifics of the compounds of formula (I) and a method of making them.

(7) The presence or absence of working examples

Pages 19-27 provide examples, but these examples are all directed toward methods of making the compounds of formula (I) and not toward the diagnosis and treatment of diseases or conditions using the compounds of formula (I).

(8) The quantity of experimentation necessary

Since every disease and disorder has its unique chemical pathway of expression, diagnosis and treatment of individual diseases and condition cannot be predicted a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine which compounds of formula (I) treats which diseases/conditions and diagnoses which diseases/conditions.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 11-22, 24-25 and 31-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(i) The term "capable of" in part (b) and (d) of claim 1 and line 3 of claim 11 is vague and indefinite, as it has been held that the recitation that an element is 'capable of' performing a function is not a positive limitation buy only requires the ability to so perform that function. It does not constitute a limitation in any patentable sense. In re Hutchison, 69 USPQ 138.

(ii) The term "derivative" in claims 4 (line 2), 8 (line 3), 14 (line 3), 32 (line 2) is vague and indefinite, as the metes and bounds of these claims are unascertainable. What is a derivative of avidin or streptavidin or amino-carboxy or EDTA? Is it a hydroxyl substituted compound, an alkyl substituted compound, a nitro substituted compound. . .? The specification does not define this phrase and one of ordinary skill in the art would not be apprised of its meaning.

(iii) The Markush language of claim 33 is vague and indefinite, as it is confusing. Why is there a semicolon between cyclohexy and DTPA? Is this a mistake, wherein the semicolon should be a comma, or does the semi-colon denote a relationship between cyclohexy and DTPA?

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-5, 8-9, 11-15, 17-19, 21-22, 25, 31, 35, 36, 38-39 are rejected under 35 U.S.C. 102(a) as being anticipated by Wilbur et al. (WO 97/29114).

Wilbur et al. exemplify a trifunctional biotin reagent, wherein tricarboxybenzene is the trifunctional cross-linking moiety, biotin, is the affinity ligand, maleimide is the biomolecule reactive moiety, an aryl iodide bonding moiety is the effector agent, and trioxadiamine (which contains 15 atoms) is the linker between each component of the reagent that provides an alpha carboxylate in linker 1. The linkers are connected to the individual components by amide bonds. The linkers contain ether groups which are hydrogen bonding atoms. Biotin binds with another

molecule with an affinity constant of 106M-1 or higher and specifically binds to avidin. See page 39.

It is respectfully pointed out that the recitation "for conjugation to a biomolecule for diagnosis and treatment of human animal conditions or diseases" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

It is furthermore respectfully pointed out that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Thus, limitations drawn to the intended use of the instant reagent have not been given patentable weight.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-7, 16, 20, 32, 34, 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilbur et al. as applied to claims 1-5, 8-9, 11-15, 17-19, 21-22, 25, 31, 35, 36, 38-39 above.

Wilbur et al. is directed toward a reagent comprising a trifunctional cross-linking moiety, an affinity ligand, an effector agent, a biomolecule reactive moiety, and three optional linkers.

Wilbur et al. is applied as discussed above. The reference lacks an exemplification of excluding linkers, chelating groups, radionuclides, preferred active esters.

On page 18, Wilbur et al. teach carboxylate active esters of hydroxysuccinimidyl and phenyl as interchangeable with maleimides. On page 23, it is taught that EDTA, DTPA, DOTA and others may provide chelates for radionulcides such as Y-90. On page 6, biotin, desthiobiotin, biotin sulfone, and iminobiotin, are taught as interchangeable affinity ligands. On pages 9-10, it is taught that trifunctional cross-linkers can be utilized without linkers.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute an ester of hydroxysuccinimidyl for the maleimide in structure 56 of Wilbur et al. because Wilbur et al. teach these biomolecule reactive moieties as interchangeable preferable compounds for conjugation to an activated biotinylation reagent.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the chelated radionuclides taught by Wilbur et al. on page 23 of the specification for the amino carboxy containing radionuclide because of the expectation of achieving similar radiotherapeutic effects and because of the expectation of achieving a radionuclide that is stabilized.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute biotin sulfone for biotin in structure 56 of Wilbur et al. because Wilbur et al. teach these biotins as interchangeable affinity ligands.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to teach structure 56 without linkers 1 and/or 2 because Wilbur et al. teach that linkers are not necessary and because of the expectation of achieving a compound that is stabilized from its medium, as it is not as reactive with it.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute homobiotin or norbiotin for the biotin taught by Wilbur et al. because adjacent homologs are considered to be obvious absent unexpected results. In re Henze, 85 USPQ 261, 263 (CCPA 1950).

Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wilbur et al. as applied to claims 1-9, 11-22, 25, 31-32, 34-39 above, and further in view of Gansoh et al. (5,286,850).

Wilbur et al. is applied as discussed above. The reference lacks preferred DTPA.

Gansoh et al. teach cyclohexyl DTPA as a radioactive ligand for radioimaging.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute cyclohexyl DTPA as taught by Gansoh et al. for DTPA in the invention of Wilbur et al. because of the expectation of achieving similar chelating effects and better chelating effects when an antibody is bound to the chelator. Furthermore, it is within the skill of an artisan in the contrast agent art to substitute one chelating agent for another.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lauren Q Wells whose telephone number is (703) 305-1878. The examiner can normally be reached on M-F (7-4:30), with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (703)305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

lqw
August 21, 2003

SREENI PADMANABHAN
PRIMARY EXAMINER

8/24/03